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13. ABSTRACT ***(Maximum 200 Words)***

Cyclooxygenase (COX)-1 and COX-2, are present in breast tumors and catalzye the conversion of arachadonic acid to prostaglandins. Prostaglandin E2 (PGE_2) has tumor and cell growth promoting activity, and is overexpressed in human breast cancer. We proposed a pilot study of celecoxib administered to women at increased breast cancer risk, defined as a projected 5 year Gail model risk of invasive breast cancer > 1.66%, as well as women with a history of ductal carcinoma in situ or invasive breast cancer. Our hypothesis is that celecoxib will be concentrated in breast fluid compared to corresponding plasma, and that it will decrease PGE_2 levels in nipple aspirate fluid (NAF) and in plasma. Our Specific Aims are to determine if 1) celecoxib is delivered to the breast, and 2) PGE2 levels in NAF and plasma increase after a 2 week course of celecoxib, then return to baseline 2 weeks after stopping the medication. Both pre- and postmenopausal women undergo nipple aspiration and blood draw three times: before, 2 weeks after starting celecoxib, and 2 weeks after stopping the medication. Each woman serves as her own control. Thus far we have enrolled 11 women on trial. NAF has been collected successfully in all subjects at each time point. PGE_2 levels were measurable in all NAF samples, and were significantly higher in NAF than in matched plasma. During the coming year, we hope is to determine if PGE_2 levels significantly decrease after celecoxib administration, and if they return to baseline 2 weeks after discontinuing medication.

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Table of Contents

INTRODUCTION

Cyclooxygenase (COX)-1 and COX-2 enzymes are present in breast tumors and convert arachadonic acid to prostaglandins. Prostaglandin E2 (PGE2) has tumor and cell growth promoting activity. Nonsteroidal anti-inflammatory medications inhibit both COX-1 and COX-2. Inhibition of COX-1 leads to a number of side effects, including gastrointestinal ulcers and renal toxicity. The attractiveness of COX-2 inhibitors is that they appear to be effective in both preventing and treating a wide variety of human tumors, yet have a very favorable toxicity profile. Celecoxib, for example, has been administered to thousands of people.

We are able to collect breast nipple aspirate fluid (NAF) noninvasively using a modified breast pump from > 99% of nonlactating adult females. The fluid contains breast epithelial cells, which give rise to breast cancer, as well as proteins and other molecules secreted from the ductal epithelium. It is our hypothesis that the expression of COX-2 and PGE2 in NAF will decrease in women at increased risk for breast cancer after a two week course of celecoxib.

Recent publications provide support for the hypothesis that an inhibitor of COX-2 would be effective in to prevent and treat breast cancer. The currently available generally accepted treatments for women at high breast cancer risk are limited to tamoxifen vs. observation. While effective, tamoxifen presents the potential risks of pulmonary embolism and uterine cancer. We propose a novel method to evaluate biomarkers of therapeutic efficacy using a safe, well tolerated medication which shows promise in the prevention of breast cancer.

BODY

Task 1. Enroll subjects on the trial.

A. Notify physicians at the University of Missouri-Columbia (UMC) and its Network Hospitals that the study has begun (Months 1-3).

I have moved to the UMC and informed USAMRMC of this. I have completed the task above.

B. Enroll subjects for initial and repeat aspirations (Months 1-34).

11 subjects have been enrolled. Nipple aspirations have been collected from 11 subjects, and 8 subjects have completed the study.

C. Work with data management programmers to establish data entry files (Months 1-6).

Done.

Task 2. Assess drug delivery and effect

A. Begin evaluation of NAF and plasma specimens. Evaluate NAF and plasma levels of COX-2 and PGE_2 (Months 3-34).

NAF and plasma levels of PGE_2 have been analyzed in ___ specimens (see results below). Since we batch these, we will soon send another groups of specimens for analysis. COX-2 analysis is done by an outside company where batching is essential to lower costs. We have therefore not yet sent samples for COX-2 analysis.

B. Finalize the analysis of specimens. Compare results in baseline vs. treated vs. washout period samples (Months 33-35).

This task will be performed later.

Table 1

PGE2 (ng/ml) Levels in NAF and Plasma

	Samples with Measurable PGE2	Range	Median
NAF	6/6	1.97-4.23	2.09
Plasma	0/6 (level < 0.1 ng/ml)		

There are insufficient samples to assess the effect of celecoxib on PGE_2.

NAF PGE_2 was measurable before and after celecoxib administration.

KEY RESEARCH ACCOMPLISHMENTS

- Collection of NAF and plasma from 11/34 projected subjects
- Successful analysis of PGE2 in NAF from all samples tested
- There has been no significant toxicity
- No subject has withdrawn from the study

REPORTABLE OUTCOMES

Statistical analysis of our results is premature.

CONCLUSIONS

The research conducted thus far indicates that 1) celecoxib is well tolerated in this subject population, 2) celecoxib does not inhibit our ability to collect NAF, 3) we can successfully recruit subjects to this trial and 4) we can analyze NAF specimens for PGE_2, and 4) plasma levels are below the sensitivity of our assay, 0.1 ng PGE_2/ml sample.

REFERENCES: N/A

APPENDICES: N/A